IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of :

Masako KIMURA et al. :

Patent No. 6,114,319 : **Mail Stop: Hatch-Waxman PTE**

Issued September 5, 2000 :

COMPOSITIONS CONTAINING DIFLUPREDNATE

PATENT OFFICE FEE TRANSMITTAL FORM

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Attached hereto is a check in the amount of $1,120.00 to cover Patent Office fees relating to filing the following attached papers:

Patent Term Extension Application $1,120.00

A duplicate copy of this paper is being submitted for use in the Accounting Division, Office of Finance.

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975, with the EXCEPTION of deficiencies in fees for multiple dependent claims in new applications.

Respectfully submitted,

Masako KIMURA et al.

By _____
Warren M. Cheek
Registration No. 33,367
Attorney for Patentees

10/28/2008 RLOGAN 00000001 09076124
01 FC:1457 1120.00 OP

WRS/WMC/lc
WENDEROTH, LIND & PONACK, L.L.P.
2033 K St., N.W., Suite 800
Washington, D.C. 20006-1021
Telephone (202) 721-8200
August 21, 2008

[Check No. 87125]

2008_1311

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of :

Masako KIMURA et al. :

Patent No. 6,114,319 : **Mail Stop: Hatch-Waxman PTE**

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2008_1311

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of :

Masako KIMURA et al. :

Patent No. 6,114,319 : Attorney Docket No. 2008_1311

Issued September 5, 2000 :

COMPOSITIONS CONTAINING DIFLUPREDNATE

TRANSMITTAL OF AN APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Box Patent Ext.
Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an APPLICATION FOR EXTENSION OF PATENT TERM (three copies with attachments thereto) of the above-captioned patent for a product approved on June 23, 2008.

[X] The APPLICATION FOR EXTENSION OF PATENT TERM is being hand-carried to the U.S. Patent and Trademark Office.

[X] A prescribed fee in the amount of $1,120.00 is required for the application presented. A check for this fee is enclosed.

The Commissioner is authorized to charge any deficiency or to credit any overpayment associated with this communication to Deposit Account No. 23-0975.

Respectfully submitted,

Masako KIMURA et al.

By _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Patentees

WMC/WRS/lc
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
August 21, 2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of	:	
Masako KIMURA et al.	:	
Patent No. 6,114,319	:	Attorney Docket No. 2008_1311
Issued September 5, 2000	:	Mail Stop: Hatch-Waxman PTE

COMPOSITIONS CONTAINING DIFLUPREDNATE

COVER LETTER FOR UNEXECUTED DECLARATION AND POWER OF ATTORNEY FORMS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Herein enclosed are unexecuted Declaration and Power of Attorney forms from Senju Pharmaceutical Co., Ltd. and Mitsubishi Chemical Corporation.

Executed copies of these forms will follow in the near future.

Respectfully submitted,

Masako KIMURA et al.

By _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Patentees

WRS/WMC/lc
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
August 21, 2008

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of :

Masako KIMURA et al. :

Patent No. 6,114,319 : Attorney Docket No. 2008_1311

Issued September 5, 2000 : Mail Stop: Hatch-Waxman PTE

COMPOSITIONS CONTAINING DIFLUPREDNATE

DECLARATION AND POWER OF ATTORNEY ACCOMPANYING APPLICATION FOR EXTENSION OF THE TERM OF UNITED STATES PATENT NO. 6,114,319 UNDER 35 U.S.C. 156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, _____, declare as follows:

1. I am ___(insert title)_____ of Senju Pharmaceutical Co., Ltd. ("Senju"), a joint owner of the entire right and title and interest in United States Patent No. 6,114,319, and the Applicants through our agent Sirion Therapeutics, Inc. in the above-identified application for extension of the term of United States Patent No. 6,114,319.

2. I am authorized to obligate Senju in this application for patent term extension under 35 U.S.C. 156.

3. I have reviewed and understand the contents of the application being submitted concurrently herewith pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.730 for extension of the patent term of United States Patent No. 6,114,319.

4. I believe that United States Patent No. 6,114,319 is subject to extension pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.710.

5. I believe that the length of extension of term of United States Patent No. 6,114,319 being claimed is justified under 35 U.S.C. 156 and the applicable regulations.

6. I believe that the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. 156 and 37 C.F.R. 1.720.

7. On behalf of Senju I appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Charles R. Watts, Reg. No. 33,142; Michael S. Huppert, Reg. No. 40,268; Jeffrey R. Filipek, Reg. No. 41,471; W. Douglas Hahm, Reg. No. 44,142; and David M. Ovedovitz, Reg. No. 45,336 who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application for extension of the patent term of United States Patent No. 6,114,319 and to transact all business in the U.S. Patent and Trademark Office connected therewith, including the filing of requests for review under 37 C.F.R. 1.181.

I further declare that all statements made herein of our own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed _____, at _____, _____.
Date City Country

_____

Name:

Title:

Address:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of	:	
Masako KIMURA et al.	:	
Patent No. 6,114,319	:	Attorney Docket No. 2008_1311
Issued September 5, 2000	:	Mail Stop: Hatch-Waxman PTE

COMPOSITIONS CONTAINING DIFLUPREDNATE

DECLARATION AND POWER OF ATTORNEY ACCOMPANYING APPLICATION FOR EXTENSION OF THE TERM OF UNITED STATES PATENT NO. 6,114,319 UNDER 35 U.S.C. 156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, _____, declare as follows:

1. I am _____(insert title)_____ of Mitsubishi Chemical Corporation ("Mitsubishi"), a joint owner of the entire right and title and interest in United States Patent No. 6,114,319, and the Applicants through our agent Sirion Therapeutics, Inc. in the above-identified application for extension of the term of United States Patent No. 6,114,319.

2. I am authorized to obligate Mitsubishi in this application for patent term extension under 35 U.S.C. 156.

3. I have reviewed and understand the contents of the application being submitted concurrently herewith pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.730 for extension of the patent term of United States Patent No. 6,114,319.

4. I believe that United States Patent No. 6,114,319 is subject to extension pursuant to 35 U.S.C. 156 and 37 C.F.R. 1.710.

5. I believe that the length of extension of term of United States Patent No. 6,114,319 being claimed is justified under 35 U.S.C. 156 and the applicable regulations.

6. I believe that the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. 156 and 37 C.F.R. 1.720.

7. On behalf of Mitsubishi I appoint Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Warren M. Cheek, Jr., Reg. No. 33,367; Nils Pedersen, Reg. No. 33,145; Charles R. Watts, Reg. No. 33,142; Michael S. Huppert, Reg. No. 40,268; Jeffrey R. Filipek, Reg. No. 41,471; W. Douglas Hahm, Reg. No. 44,142; and David M. Ovedovitz, Reg. No. 45,336 who together constitute the firm of WENDEROTH, LIND & PONACK, L.L.P., as well as any other attorneys and agents associated with Customer No. 000513, to prosecute this application for extension of the patent term of United States Patent No. 6,114,319 and to transact all business in the U.S. Patent and Trademark Office connected therewith, including the filing of requests for review under 37 C.F.R. 1.181.

I further declare that all statements made herein of our own knowledge are true, and that all statements on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed _____, at _____, _____.
Date City Country

_____

Name:

Title:

Address:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of	:	
Masako KIMURA et al.	:	
Patent No. 6,114,319	:	Attorney Docket No. 2008_1311
Issued September 5, 2000	:	Mail Stop: Hatch-Waxman PTE

COMPOSITIONS CONTAINING DIFLUPREDNATE

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Box Patent Ext.
Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to § 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, SENJU PHARMACEUTICAL CO. LTD, of Osaka-shi 5-8, Hiranomachi 2-chome, Chuo-ku, Osaka 541-0046, Japan and MITSUBISHI CHEMICAL CORPORATION of 14-1, Shiba 4-Chome, Minato-ku, Tokyo 108-0014, Japan, the Assignees and Owners of record of the patent, hereby request an extension to the term of United States Patent No. 6,114,319 of 369 days, thereby setting the expiration of this patent to May 16, 2019.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740, and follows the numbering format set forth in 37 C.F.R. § 1.740.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

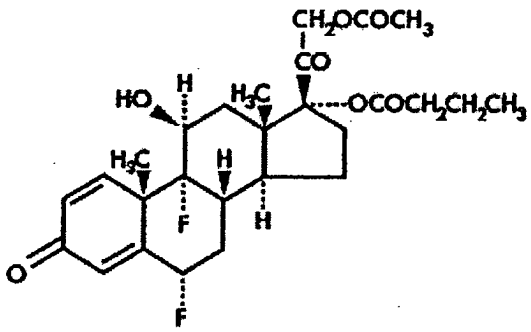
The approved product is Durezol™ (difluprednate ophthalmic emulsion) 0.05%. Durezol™ is a topical corticosteroid and is indicated for the treatment of inflammation and pain associated with ocular surgery.

Durezol™ (difluprednate ophthalmic emulsion) 0.05% is a sterile, aqueous topical ophthalmic emulsion supplied in an opaque plastic bottle with a controlled drop tip and a pink cap in the following sizes:

– 2.5 mL in a 5 mL bottle (NDC 42826-601-25)

– 5 mL in a 5 mL bottle (NDC 42826-601-05)

Durezol™ (difluprednate ophthalmic emulsion) 0.05% is a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. The chemical name is 6α,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate (CAS number 23674-86-4). Difluprednate is represented by the following structural formula:



Difluprednate has a molecular weight of 508.56, and the empirical formula is $C_{27}H_{34}F_2O_7$.

Each mL contains: ACTIVE: difluprednate 0.5 mg (0.05%); INACTIVES: boric acid, castor oil, glycerin, polysorbate 80, purified water, sodium acetate, sodium EDTA, sodium hydroxide (to adjust the pH to 5.2 to 5.8). The emulsion is essentially isotonic with a tonicity of 304 to 411 mOsm/kg. PRESERVATIVE: sorbic acid 0.1%.

Durezol™ is further described in Exhibit 1.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review of Durezol™ occurred under § 505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 301 et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

Durezol™ was approved by the Food and Drug Administration ("FDA") pursuant to § 505(b) of the FFDCA on June 23, 2008; see Exhibit 2 (NDA Approval).

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in the approved Durezol™ formulation is difluprednate. Difluprednate (6α,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate (CAS number 23674-86-4)), either alone or in combination with other active ingredients, has not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § l.720(f) and an identification of the date of the last day on which the application could be submitted:

Durazol™ was approved for commercial marketing on June 23, 2008. Thus, counting June 23, 2008 as the first day, the last day within the sixty day period permitted for submission of an application for extension of the patent is August 21, 2008. The date of submission of the present application is no later than August 21, 2008. Thus, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. PATENT NUMBER:	6,114,319
INVENTORS:	Masako Kimura
	Shin-ichi Yasueda
	Masazumi Yamaguchi
	Katsuhiro Inada
ISSUE DATE:	September 5, 2000
EXPIRATION DATE:	May 12, 2018

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings:

A copy of U.S. Patent 6,114,319 is attached as Exhibit 3 (PATENT).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

No disclaimer or certificate of correction has been issued. A copy of a Reexamination Certificate is attached in Exhibit 4. A copy of the receipts showing the first and second maintenance fees being paid are attached as Exhibit 5.

(9) A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product;

(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product.

The approved product Durezol™ is covered by granted U.S. Patent No. 6,114,319 (granted 5 September 2000) assigned to Senju Pharmaceutical Co., Ltd. and Mitsubishi Chemical Corporation.

Claims of US 6,114,319 as issued after re-examination

1. A difluprednate emulsion in the form of an eye drop, a nasal drop or an ear drop comprising (a) difluprednate, (b) an oil selected from the group consisting of castor oil, peanut oil, cotton-seed oil, soybean oil, olive oil and a medium chain fatty acid triglyceride, (c) water and (d) an emulsifier.
2. The emulsion of claim 1, comprising 10-100,000 parts by weight of oil, 100-100,000 parts by weight of water and 10-100,000 parts by weight of the emulsifier, per part by weight of difluprednate.

3. The emulsion of claim 1, comprising 10-10,000 parts by weight of oil, 100-50,000 parts by weight of water and 10-10,000 parts by weight of the emulsifier, per part by weight of difluprednate.
4. The emulsion of claim 1, comprising 10-5,000 parts by weight of oil, 500-50,000 parts by weight of water and 10-5,000 parts by weight of the emulsifier, per part by weight of difluprednate.
5. (Cancelled).
6. The emulsion of claim 1, wherein the emulsifier comprises a surfactant.
7. The emulsion of claim 6, wherein the surfactant is a nonionic surfactant.
8. The emulsion of claim 7, wherein the nonionic surfactant is a member selected from the group consisting of polyoxyethylene hydrogenated castor oil and a polyoxyethylenesorbitan fatty acid ester.
9. The emulsion of claim 8, wherein the polyoxyethylenesorbitan fatty acid ester is a member selected from the group consisting of polyoxyethylenesorbitan monooleate, polyoxyethylenesorbitan monolaurate, polyoxyethylenesorbitan monopalmitate and polyoxyethylenesorbitan monostearate.
10. The emulsion of claim 1 which is an oil-in-water type emulsion.
11. (Cancelled).
12. The emulsion of claim 2, which is an oil-in-water type emulsion.
13. The emulsion of claim 3, which is an oil-in-water type emulsion.
14. The emulsion of claim 4, which is an oil-in-water type emulsion.
15. (Cancelled).
16. (Cancelled).
17. (Cancelled).
18. A difluprednate emulsion in the form of an eye drop, a nasal drop or an ear drop comprising difluprednate, castor oil, water and polyoxyethylene (20) sorbitan monooleate.

Claims that read on the approved product

Claim 1 reads on a difluprednate emulsion in the form of an eye drop, a nasal drop or an ear drop comprising difluprednate, an oil selected from the group consisting of castor oil, peanut oil, cotton-seed oil, soybean oil, olive oil and a medium chain fatty acid triglyceride, water and an emulsifier. The approved product is an eye drop emulsion containing difluprednate, boric acid, castor oil, glycerin, polysorbate 80, purified water, sodium acetate, sodium EDTA, sodium hydroxide and sorbic acid 0.1%. Thus, the approved product contains difluprednate, castor oil, water and the emulsifier polysorbate 80 and therefore this claim reads on the approved product.

Claim 2 is directed towards the emulsion of claim 1, comprising 10-100,000 parts by weight of oil, 100-100,000 parts by weight of water and 10-100,000 parts by weight of the emulsifier, per part by weight of difluprednate. As shown in Exhibit 1, the approved composition per 0.5 mg difluprednate contains 50 mg castor oil (100 parts) and 40.0 mg polysorbate 80 (80 parts). Further, water is added to *q.s.* to 1 ml. Thus, the amount of water necessary falls between 250 µl (250 mg which equals 500 parts) and >1000 µl (1000 mg which is 2000 parts). Thus, this claim reads on the approved product.

Claim 3 is directed towards the emulsion of claim 1, comprising 10-10,000 parts by weight of oil, 100-50,000 parts by weight of water and 10-10,000 parts by weight of the emulsifier, per part by weight of difluprednate. As noted above, the approved product contains 100 parts oil, 80 parts emulsifier and 500-2000 parts water. Thus, this claim reads on the approved product.

Claim 4 is directed towards the emulsion of claim 1, comprising 10-5,000 parts by weight of oil, 500-50,000 parts by weight of water and 10-5,000 parts by weight of the emulsifier, per part by weight of difluprednate. As noted above, the approved product contains 100 parts oil, 80 parts emulsifier and 500-2000 parts water. Thus, this claim reads on the approved product.

Claim 6 is directed towards the emulsion of claim 1 wherein the emulsifier is a surfactant. Polysorbate 80 is a surfactant. Therefore this claim reads on the approved product.

Claim 7 is directed towards the emulsion of claim 6 wherein the surfactant is a nonionic surfactant. Polysorbate 80 is a nonionic surfactant. Therefore this claim reads on the approved product.

Claims 10 and 12-14 are directed towards the emulsions of claims 1, 2, 3 and 4, respectively, wherein the emulsion is an oil-in-water type emulsion. The approved product meets the limitations of claims 1-4 and is an oil-in-water type emulsion. Therefore these claims read on the approved product.

Claim 18 is directed towards a difluprednate emulsion in the form of an eye drop, a nasal drop or an ear drop comprising difluprednate, castor oil, water and polyoxyethylene (20) sorbitan monooleate. The approved product is an eye drop emulsion containing difluprednate, boric acid, castor oil, glycerin, polysorbate 80 (chemical name: polyoxyethylene (20) sorbitan monooleate), purified water, sodium acetate, sodium EDTA, sodium hydroxide and sorbic acid 0.1%. The approved product contains difluprednate, castor oil, water and polyoxyethylene (20) sorbitan monooleate. Therefore this claim reads on the approved product.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C.156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued;

On November 9, 2006, Sirion Therapeutics Inc., the Marketing Applicant for the patent Assignees, submitted to the Food and Drug Administration an Investigational New Drug application (IND) for difluprednate ophthalmic emulsion, 0.05% (ST-601A), now Durezol™. A copy of the letter accompanying the IND submission is Exhibit 6. The IND was received by the FDA on November 13, 2006 and assigned IND number 75,713. The IND became effective on December 13, 2006, as evidenced by Exhibit 7. This establishes the beginning of the "regulatory review period" under 35 U.S.C. § 156(g)(1) as December 13, 2006.

On December 21, 2007, a New Drug Application (NDA) was submitted under § 505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and 21 C.F.R. § 314 by Sirion Therapeutics, Inc. A copy of the cover letter attached to the NDA is Exhibit 8. The NDA was received by the FDA on December 26, 2007 (initial submission date) and assigned reference number NDA 22-212, as shown in Exhibit 9.

The NDA was approved on June 23, 2008, see Exhibit 2. Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. § 156(g)(1), the date of first approval of Durezol™ is June 23, 2008.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), the IND for Durezol™ became effective December 13, 2006. The clinical studies under the IND are summarized in the attached Exhibit 10. These clinical studies were used to support NDA 22-212 submitted on December 21, 2007.

Subsequent to the submission of the NDA, applicants' agent and Marketing Applicant, Sirion Therapeutics, Inc. had numerous contacts and meetings with the FDA with respect to the application and these are also summarized Exhibit 10.

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension
Under 35 U.S.C. § 156(a) and (c)(4)

(1) The statutory term of U.S. Patent No. 6,114,319 expires on May 12, 2018 (twenty years from the filing date). The present Application has, therefore, been submitted before the expiration of the patent term. All required maintenance fees have been paid. (See Exhibit 5).

(2) The term of this patent has never been extended under subsection (e)(1) of 35 U.S.C. § 156.

(3) This Application is submitted by Senju Pharmaceutical Co., Ltd and Mitsubishi Chemical Corporation, owners of record of Patent 6,114,319, by an assignment recorded at Reel 009369, Frame 0995, on May 12, 1998. See Exhibit 11. This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date, June 23, 2008, that the Durezol™ product received permission for marketing under the Federal Food, Drug and Cosmetic Act and this application contains the information required under 35 U.S.C. § 156(d).

(4) As evidenced by the letter from the FDA dated June 23, 2008, see Exhibit 2, the Durezol™ product was subject to a regulatory review period under § 505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of Durezol™ after regulatory review under § 505(b) is the first permitted commercial marketing of the approved product.

(6) No other U.S. patent has been extended under subsection (e)(1) of 35 U.S.C. § 156 for this regulatory review period for any product.

Statement as to Length of Extension Claimed

In Accordance with 37 C.F.R. § 1.775

The term of U.S. Patent No. 6,114,319 should be extended for a period of 369 days to May 16, 2019.

The period of extension is determined in accordance with 35 U.S.C. § 156 and follows the format set forth in 37 C.F.R. § 1.775(c) and (d).

37 C.F.R. § 1.775 (c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. § 156(g)(1)(B), it is the sum of —

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date an application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act;

The number of days between the effective date of the IND, December 13, 2006, and the initial submission of the NDA, December 26, 2007(date of receipt by the FDA), is a period of 378 days.

and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the initial submission of the NDA, December 26, 2007, to NDA approval, June 23, 2008, is a period of 180 days.

37 C.F.R. § 1.775 (d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by—

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on December 13, 2006, which were on or before the date on which the patent issued, September 5, 2000, is a period of 0 days.

378 days minus 0 days equals 378 days;

and

the number of days in the period of the NDA, initially submitted on December 26, 2007, which were on or before the date the patent was issued, September 5, 2000, is a period of 0 days.

180 days minus 0 days is 180 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;

Applicants submit it was diligent in all matters involving Durezol™. Applicants further submit that through its agent Marketing Applicant Sirion Therapeutics, it was continuously and diligently working toward securing NDA approval for Durezol™. Accordingly the number of days Applicants did not act with due diligence is 0 days. Applicants note that a chronology of significant activities during the review period is shown in Exhibit 10.

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One-half of 378 days equals 189 days. Thus, U.S. Patent No. 6,114,319 should be entitled to an extension of 369 days (189 plus 180).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 369 days to May 12, 2018, the original term of the patent (no terminal disclaimer was made), extends the term to May 16, 2019.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to June 23, 2008, the date of approval of the NDA, gives the date of June 23, 2022.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is May 16, 2019.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer;

Adding 5 years to the original expiration date of the patent (May 12, 2018) gives the date of May 12, 2023.

and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

The earlier date is May 16, 2019, and the patent term should therefore be extended to May 16, 2019.

(6) If the original patent was issued before September 24, 1984,

This is not applicable for the patent.

(13) A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see § 1.765):

Applicants acknowledge a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicants are unaware of any additional information material to this Application for extension.

(14) The prescribed fee for receiving and acting upon the application for extension (see § 1.20(j)):

The prescribed fee of $1,120.00 for receiving and acting on this application for extension of patent term is attached. Please charge Deposit Account No. 23-0975 for any greater amount as the Commissioner determines is required by law.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Warren M. Cheek, Jr.
Registration No. 33,367
Partner,
Wenderoth, Lind & Ponack, L.L.P.
2033 K Street, N.W.
Suite 800
Washington, D.C. 20006-1021
Tel: (202) 721-8200
Fax: (202) 721-8250

The undersigned hereby certifies that this application for extension of patent term under 35 U.S.C. 156, including its attachments and supporting papers, is being submitted with two additional copies of such application.

Respectfully submitted,

Masako KIMURA et al.

By _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Patentees

WMC/WRS/lc
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
August 21, 2008

EXHIBIT 1

1. Identification of Product

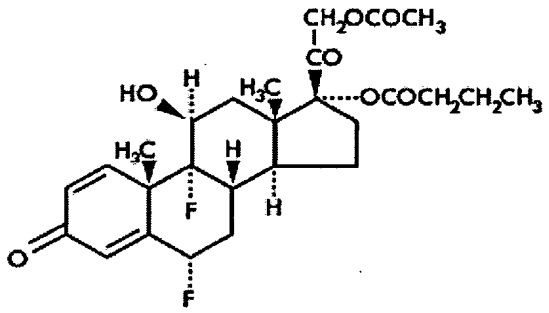
Name of Approved Product: Durezol™ (difluprednate ophthalmic emulsion) 0.05%.

Durezol (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.

Durezol (difluprednate ophthalmic emulsion) 0.05% is a sterile, aqueous topical ophthalmic emulsion supplied in an opaque plastic bottle with a controlled drop tip and a pink cap in the following sizes:

- 2.5 mL in a 5 mL bottle (NDC 42826-601-25)
- 5 mL in a 5 mL bottle (NDC 42826-601-05)

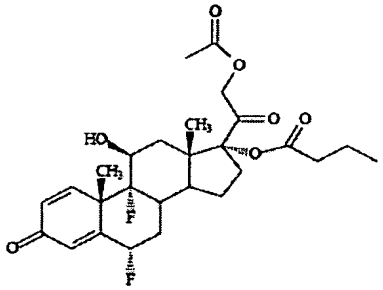
Durezol (difluprednate ophthalmic emulsion) 0.05% is a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. The chemical name is 6α,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate (CAS number 23674-86-4). Difluprednate is represented by the following structural formula:



Difluprednate has a molecular weight of 508.56, and the empirical formula is C27H34F2O7.

Each mL contains: ACTIVE: difluprednate 0.5 mg (0.05%); INACTIVES: boric acid, castor oil, glycerin, polysorbate 80, purified water, sodium acetate, sodium EDTA, sodium hydroxide (to adjust the pH to 5.2 to 5.8). The emulsion is essentially isotonic with a tonicity of 304 to 411 mOsm/kg. PRESERVATIVE: sorbic acid 0.1%.

2.3.S.1 GENERAL INFORMATION

USAN:	Difluprednate
INN:	Difluprednate
Chemical name:	6α, 9-Difluoro-11β,17.21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate
Proprietary name:	NA
Company codes:	DFBA
CAS registry number:	23674-86-4
Structural Formula: (Relative stereochemistry)	
Structural formula: (Absolute stereochemistry)	Refer to the Type II DMF 19870 filed by Sicor for the absolute stereochemical structure of Difluprednate
Molecular formula:	$C_{27}H_{34}F_2O_7$
Molecular weight:	508.56

2.3.P.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

Table 2 provides the quantitative composition of ST-601 (difluprednate ophthalmic emulsion, 0.05%), with the function of each of the components in the drug product.

Table 2. Composition of the ST-601 Drug Product (per mL)

Components	Function	Weight (mg/mL)	% w/v
Difluprednate	Active ingredient	0.5	0.05%
Polysorbate 80	Emulsifier	40.0	4.0%
Glycerin	Tonicity	22.0	2.2%
Sorbic acid	Preservative	1.0	0.1%
Sodium acetate, anhydrous	Buffer	0.5	0.05%
Boric acid	Buffer	1.0	0.1%
Sodium EDTA	Stabilizer	0.2	0.02%
Castor oil	Oil phase	50.0	5.0%
Water for injection	Water phase	qs 1 mL	-
Sodium hydroxide	pH adjustment	As needed	As needed

qs, sufficient quantity

The ST-601 composition presented in Table 2 represents the formulation used in the US clinical studies, as well as the Senju ophthalmic clinical studies (see 5.2 for the tabular listing of the clinical studies) and the nonclinical ophthalmic safety studies (see 2.6.7 for a list of the nonclinical safety studies).

EXHIBIT 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-212

NDA APPROVAL

Sirion Therapeutics, Inc.
Attention: Christine Miller, PharmD
Senior Vice President of Drug Development
3110 Cherry Palm Drive, Suite 340
Tampa, FL 33619

Dear Dr. Miller:

Please refer to your new drug application (NDA) dated December 21, 2007, received December 26, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Durezol (difluprednate ophthalmic emulsion) 0.05%.

We acknowledge receipt of your submissions dated January 23, March 18, April 18, 25 and 28, May 8, 14, 15, 19 and 30, and June 10, 11, 18 (2) and 23, 2008.

This new drug application provides for the use of Durezol (difluprednate ophthalmic emulsion) 0.05% for treatment of inflammation and pain associated with ocular surgery.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert), submitted June 23, 2008. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 22-212.**"

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-212**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 to 16 years, 11 months until June 26, 2011.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of treatment of post-operative inflammation following cataract surgery in pediatric patients aged 0 to 3 years of age undergoing cataract surgery.

2. Final Report Submission: June 26, 2011

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

POSTMARKETING COMMITMENTS

We remind you of your postmarketing study commitment in your submission dated June 10, 2008. This commitments is listed below.

1. Description of Commitment – post-marketing study of difluprednate in pediatric subjects

Protocol Submission:	by 10/26/2008
Study Start:	by 01/26/2009
Final Report Submission:	by 06/26/2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Edward Cox, MD
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use Durezol safely and effectively. See full prescribing information for Durezol.
Durezol (difluprednate ophthalmic emulsion) 0.05%

Initial U.S. approval: 2008

----------INDICATIONS AND USAGE----------

Durezol is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery. (1)

----------DOSAGE AND ADMINISTRATION----------

Instill one drop into the conjunctival sac of the affected eye(s) 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Durezol contains 0.05% difluprednate, as a sterile preserved ophthalmic emulsion for topical ophthalmic use only. (3)

----------CONTRAINDICATIONS----------

Durezol, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. (4)

----------WARNINGS AND PRECAUTIONS----------

- Intraocular pressure (IOP) increase-Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored. (5.1).
- Cataracts- Use of corticosteroids may result in posterior subcapsular cataract formation. (5.2)
- Delayed healing- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. (5.3)
- Bacterial infections- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated. (5.4)
- Viral infections- Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). (5.5)
- Fungal infections- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. (5.6)

To report SUSPECTED ADVERSE REACTIONS, contact Sirion Therapeutics at (TBD) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised date: June 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 Indications and Usage

Durezol (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.

2 Dosage and Administration

Instill one drop into the conjunctival sac of the affected eye(s) 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response. (2)

3 Dosage Forms and Strengths

Durezol contains 0.05% difluprednate as a sterile preserved emulsion for topical ophthalmic administration.

4 Contraindications

The use of Durezol, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

5 Warnings and Precautions

5.1 IOP Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 Bacterial infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

5.5 Viral infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

5.6 Fungal infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal culture should be taken when appropriate.

5.7 Topical ophthalmic use only

Durezol is not indicated for intraocular administration.

6 Adverse Reactions

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Ocular adverse reactions occurring in 5–15% of subjects in clinical studies with Durezol included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1–5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse events occurring in < 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, scleral hyperemia, and uveitis. Most of these events may have been the consequence of the surgical procedure.

8 Use in Specific Populations

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C. Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal anomalies when administered subcutaneously to rabbits during organogenesis at a dose of 1–10 µg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 µg/kg/day, and 10 µg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 µg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 µg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of Durezol, since Durezol is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, Durezol should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

8.3 Nursing Mothers

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Durezol is administered to a nursing woman.

8.4 Pediatric Use

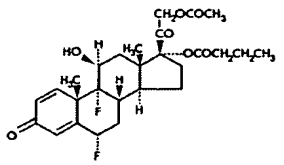
Safety and effectiveness in pediatric patients has not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 Description

Durezol (difluprednate ophthalmic emulsion) 0.05% is a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. The chemical name is 6α,9-difluoro-11β,17,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate (CAS number 23674-86-4). Difluprednate is represented by the following structural formula:



Difluprednate has a molecular weight of 508.56, and the empirical formula is $C_{27}H_{34}F_2O_7$.

Each mL contains: ACTIVE: difluprednate 0.5 mg (0.05%); INACTIVES: boric acid, castor oil, glycerin, polysorbate 80, purified water, sodium acetate, sodium EDTA, sodium hydroxide (to adjust the pH to 5.2 to 5.8). The emulsion is essentially isotonic with a tonicity of 304 to 411 mOsm/kg. PRESERVATIVE: sorbic acid 0.1%.

12 Clinical Pharmacology

12.1 Mechanism of Action

Corticosteroids inhibit the inflammatory response to a variety of inciting agents that may delay or slow healing. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of

inflammation such as prostaglandins and leukotreines by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Difluprednate is structurally similar to other corticosteroids.

12.3 Pharmacokinetics

Difluprednate undergoes deacetylation in vivo to 6α,9-difluoroprednisolone 17-butyrate (DFB), an active metabolite of difluprednate.

Clinical pharmacokinetic studies of difluprednate after repeat ocular instillation of 2 drops of difluprednate (0.01% or 0.05%) QID for 7 days showed that DFB levels in blood were below the quantification limit (50 ng/mL) at all time points for all subjects, indicating the systemic absorption of difluprednate after ocular instillation of Durezol is limited.

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Difluprednate was not genotoxic in vitro in the Ames test, and in cultured mammalian cells CHL/IU (a fibroblastic cell line derived from the lungs of newborn female Chinese hamsters). An *in vivo* micronucleus test of difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 µg/kg/day prior to and during mating did not impair fertility in either gender. Long term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

13.2 Animal Toxicology and/or Pharmacology

In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicity tests of difluprednate showed systemic effects such as suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin; all of which were due to the pharmacologic action of the molecule and are well known glucocorticosteroid effects. Most, if not all of these effects were reversible after drug withdrawal. The NOEL for the subchronic and chronic toxicity tests were consistent between species and ranged from 1–1.25 µg/kg per day.

14 Clinical Studies

14.1 Postoperative Ocular Inflammation and Pain

Clinical efficacy was evaluated in 2 randomized, double-masked, placebo-controlled trials in which subjects with an anterior chamber cell grade ≥ "2" (a cell count of 10 or higher) after cataract surgery were assigned to Durezol or placebo (vehicle) following surgery. One drop of Durezol or vehicle was self instilled either 2 (BID) or 4 (QID) times per day for 14 days, beginning the day after surgery. The presence of complete clearing (a cell count of 0) was assessed 8 and 15 days post-surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies, a significant benefit was seen in the QID Durezol-treated group in ocular inflammation and reduction of pain when compared with placebo. The consolidated clinical trial results are provided below.

Ocular Inflammation and Pain Endpoints (Studies Pooled)

	Durezol QID N = 107		Vehicle N = 220	
Day	8	15	8	15
Anterior Chamber cell clearing (% subjects)	24 (22%)*	44 (41%)*	17 (7%)	25 (11%)
Pain free (% subjects)	62 (58%)*	67 (63%)*	59 (27%)	76 (35%)

* Statistically significantly better than vehicle, $p<0.01$

16 How Supplied/Storage and Handling

Durezol (difluprednate ophthalmic emulsion) 0.05% is a sterile, aqueous topical ophthalmic emulsion supplied in an opaque plastic bottle with a controlled drop tip and a pink cap in the following sizes:

- 2.5 mL in a 5 mL bottle (NDC 42826-601-25)
- 5 mL in a 5 mL bottle (NDC 42826-601-05)

Storage

Store at 15-25°C (59-77°F). Do not freeze. Protect from light. When not in use keep the bottles in the protective carton and the unused vials in the protective foil pouch.

Revised: June 2008

17 Patient Counseling Information

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the emulsion. If pain develops or if redness, itching, or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing a preservative, patients should be advised not to wear contact lenses when using Durezol.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Cox
6/23/2008 04:59:44 PM

EXHIBIT 3

US006114319A

United States Patent [19]

Kimura et al.

[11] Patent Number: 6,114,319

[45] Date of Patent: Sep. 5, 2000

[54] **COMPOSITIONS CONTAINING DIFLUPREDNATE**

[75] Inventors: **Masako Kimura**, Kakogawa; **Shin-ichi Yasueda**, Kobe; **Masazumi Yamaguchi**, Kobe; **Katsuhiro Inada**, Kobe, all of Japan

[73] Assignees: **Senju Pharmaceutical Co., Ltd.**; **Mitsubishi Chemical Corporation**, both of Japan

[21] Appl. No.: **09/076,124**

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[58] **Field of Search** 514/177, 912

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,780,177 12/1973 Ercoli et al. .

4,427,670 1/1984 Ofuchi et al. .

5,556,848 9/1996 Kimura et al. 514/179

FOREIGN PATENT DOCUMENTS

5-43465 2/1993 Japan .

WO98/30221 7/1998 WIPO .

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[57] **ABSTRACT**

The present invention relates to a liquid composition comprising difluprednate, oil, water and an emulsifier. The composition of the present invention has superior antiinflammatory action and antiallergic action. The composition of the present invention shows superior transfer to a lesion and uniform drug distribution upon administration, as compared to conventional preparations containing difluprednate, so that it shows sufficient efficacy in a smaller dose. The inventive composition is associated with extremely less uncomfortable feeling and foreign sensation upon administration, as compared to conventional preparations containing difluprednate, and it can be administered easily to local sites of eye, nose, ear and the like.

17 Claims, No Drawings

COMPOSITIONS CONTAINING DIFLUPREDNATE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a liquid composition containing difluprednate, oil, water and an emulsifier. More particularly, the present invention relates to a liquid composition containing difluprednate, which permits uniform drug distribution and superior transfer of difluprednate into a lesion, and which is associated with less uncomfortable feeling and foreign sensation.

BACKGROUND OF THE INVENTION

Difluprednate (6α,9α-difluoroprednisolone 17-butyrate 21-acetate) is an antiinflammatory steroid which is known to show superior antiinflammatory action by percutaneous administration (U.S. Pat. Nos. 3,780,177, 3,784,692). In addition, difluprednate is reported to show superior antiinflammatory action and antiallergic action by percutaneous administration and subcutaneous administration (Pharmacometrics, 29 (3), 343–353 (1985), Pharmacometrics, 29 (3), 355–362 (1985)). Therefore, difluprednate is mainly used as a therapeutic drug in the preparation form of ointment, cream and the like for skin disorders.

On the other hand, when difluprednate is administered locally to an eye, nose, ear or the like, a liquid dosage form, such as an eye drop, a nasal drop, an ear drop and the like, is desirable. However, inasmuch as difluprednate has extremely low solubility in water, it is difficult to prepare a stable eye drop, nasal drop, ear drop or the like, containing difluprednate in a concentration effective for treatment, and a dosage form of an aqueous suspension has been proposed for the administration to the local sites as mentioned above (U.S. Pat. No. 5,556,848).

When, for example, an aqueous suspension of difluprednate is used as an eye drop, however, common problems associated with aqueous ophthalmic suspensions, namely, difficulty in sustaining uniform drug distribution upon instillation, uncomfortable feeling caused by solid entering into the eye and inability to completely eliminate foreign sensation, have been pointed out. In addition, since difluprednate is an antiinflammatory steroid, it is on the one hand sufficiently effective for the treatment of inflammatory diseases, allergic diseases and the like, but on the other hand associated with side effects. Thus, there is a need for the development of a dosage form permitting quick and uniform transfer of an effective amount of difluprednate and causing less side effects, in view of a case where a part (e.g., inner ocular area) distant from the instillation site (e.g., outer ocular area) has an inflammation.

SUMMARY OF THE INVENTION

As mentioned above, since difluprednate has superior antiinflammatory action and antiallergic action, it is useful for the prophylaxis and treatment of various inflammatory diseases and allergic diseases. When it is applied for the treatment of diseases in the eye, nose, ear and the like, it needs to be formulated into an administration dosage form permitting instillation in the eye, nose, ear and the like. When difluprednate is used in the form of an aqueous suspension for the treatment of these local diseases, however, the above-mentioned problems in terms of transfer of the drug to the lesion, distribution of the drug and feeling in use, such as uncomfortable feeling and foreign sensation, remain to be solved.

It is therefore an object of the present invention to provide a composition containing difluprednate, which shows superior transfer of the drug to the lesion, uniform drug distribution upon administration, less uncomfortable feeling and foreign sensation upon administration, and less side effects.

According to the present invention, it has now been found that a dosage form of a liquid composition containing difluprednate, oil, water and an emulsifier results in quick transfer of a large amount of difluprednate, uniform drug distribution and extremely reduced levels of uncomfortable feeling and foreign sensation upon local administration to the eye, nose, ear and the like. Inasmuch as difluprednate can be transferred smoothly, administration of a small dose thereof is sufficient to bring about efficacy, whereby side effects can be suppressed.

That is, the present invention provides the following.

(1) A difluprednate liquid composition comprising difluprednate, oil, water and an emulsifier.

(2) The composition of (1) above, comprising 10–100,000 parts by weight of oil, 100–100,000 parts by weight of water and 10–100,000 parts by weight of the emulsifier, per part by weight of difluprednate.

(3) The composition of (1) above, comprising 10–10,000 parts by weight of oil, 100–50,000 parts by weight of water and 10–10,000 parts by weight of the emulsifier, per part by weight of difluprednate.

(4) The composition of (1) above, comprising 10–5,000 parts by weight of oil, 500–50,000 parts by weight of water and 10–5,000 parts by weight of the emulsifier, per part by weight of difluprednate.

(5) The composition of (1) above, wherein the oil comprises a fatty acid ester of glycerol.

(6) The composition of (5) above, wherein the fatty acid ester of glycerol is a member selected from the group consisting of castor oil, peanut oil, cotton seed oil, soybean oil, olive oil and a medium chain fatty acid triglyceride.

(7) The composition of (1) above, wherein the emulsifier comprises a surfactant.

(8) The composition of (7) above, wherein the surfactant is a nonionic surfactant.

(9) The composition of (8) above, wherein the nonionic surfactant is a member selected from the group consisting of polyoxyethylene hydrogenated castor oil and a polyoxyethylenesorbitan fatty acid ester.

(10) The composition of (9) above, wherein the polyoxyethylenesorbitan fatty acid ester is a member selected from the group consisting of polyoxyethylene-sorbitan monooleate, polyoxyethylenesorbitan monolaurate, polyoxyethylene-sorbitan monopalmitate and polyoxyethylenesorbitan monostearate.

(11) The composition of any one of (1) to (4) above, which is an oil-in-water type emulsion.

(12) The composition of any one of (1) to (4) above, which is in the form of an eye drop, a nasal drop or an ear drop.

DETAILED DESCRIPTION OF THE INVENTION

The composition of the present invention contains difluprednate, oil, water and an emulsifier. The oil usable in the present invention may be any as long as it is applicable to the eye, and is low toxic and less irritant to the eye. Preferably, an oil containing a fatty acid ester of glycerol, such as castor oil, peanut oil, cotton seed oil, soybean oil, olive oil, medium chain fatty acid triglycerides (e.g., Miglyol, trademark, manufactured by Mitsuba Boeki) and the like, is used. More preferably, castor oil, medium chain

fatty acid triglycerides (e.g., Miglyol) and the like, in which difluprednate is highly soluble, can be used.

In the present invention, a surfactant, such as a nonionic surfactant having surface activating capability and the like, may be contained as an emulsifier. Examples of the nonionic surfactant include polyoxyethylene hydrogenated castor oils and polyoxyethylenesorbitan fatty acid esters, preferably polyoxyethylenesorbitan monooleates, polyoxyethylenesorbitan monolaurates, polyoxyethylenesorbitan monopalmitates, polyoxyethylenesorbitan monostearates and the like.

While the ratio of each of the above-mentioned ingredients in the composition of the present invention is not particularly limited, it is preferable that oil be contained in a proportion of 10–100,000 parts by weight, water in a proportion of 100–100,000 parts by weight and emulsifier in a proportion of 10–100,000 parts by weight, all per part by weight of difluprednate; preferably in the proportions of oil 10–10,000 parts by weight, water 100–50,000 parts by weight and emulsifier 10–10,000 parts by weight, all per part by weight of difluprednate; and particularly preferably in the proportions of oil 10–5,000 parts by weight, water 500–50,000 parts by weight and emulsifier 10–5,000 parts by weight, all per part by weight of difluprednate.

It is particularly preferable that the weight ratio of water (which is a medium) to oil be 4:1–99:1.

The composition of the present invention may contain a water soluble polymer for enhanced stabilization of emulsion. Examples of the water soluble polymer include povidone (polyvinylpyrrolidone), polyvinyl alcohol, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose and salt thereof, and the like.

The composition of the present invention may contain a buffer. Examples of the buffer include acetates such as sodium acetate and the like, phosphates such as sodium dihydrogenphosphate, disodium hydrogenphosphate, potassium dihydrogenphosphate, dipotassium hydrogenphosphate and the like, ϵ-aminocaproic acid, amino acid salts such as sodium glutamate and the like, boric acid and salt thereof, citric acid and salt thereof, and the like.

The composition of the present invention may contain a preservative. Examples of the preservative include quaternary ammonium salts such as benzalkonium chloride, benzethonium chloride and the like; cationic compounds such as chlorhexidine gluconate and the like; p-hydroxybenzoates such as methyl p-hydroxybenzoate, propyl p-hydroxybenzoate and the like; alcohol compounds such as chlorobutanol, benzyl alcohol and the like; sodium dehydroacetate; thimerosal; sorbic acid; and the like.

The composition of the present invention may contain an isotonizing agent. Examples of the isotonizing agent include sodium chloride, glycerol, glucose, mannitol, sorbitol and the like.

The composition of the present invention may also contain various additives, such as a stabilizer, an antioxidant, a chelating agent, a pH adjusting agent, a thickener and the like. Examples of the antioxidant include ascorbic acid and salt thereof, tocopherol, sodium thiosulfate, sodium hydrogensulfite, pyruvic acid and salt thereof, and the like. The chelating agent is exemplified by sodium edetate, citric acid and salt thereof, and the like. Examples of the pH adjusting agent include hydrochloric acid, phosphoric acid, acetic acid, sulfuric acid, sodium hydroxide, potassium hydroxide, sodium carbonate, sodium hydrogencarbonate, aqueous ammonia and the like.

The composition of the present invention can be provided as an aqueous preparation of oil-in-water type (O/W type) emulsion, microemulsion and the like.

An oil drop of the composition of the present invention has a median size of preferably 5–0.0001 μm, more preferably 1–0.001 μm, and particularly preferably 1–0.01 μm. The median size can be measured by an apparatus for particle size distribution.

The composition of the present invention preferably has a pH of 3–8. More preferable pH is 4–7, at which difluprednate is more stabilized.

The composition of the present invention is prepared by emulsifying oil, in which difluprednate has been dissolved, and water, using an emulsifier according to a known method. For example, an emulsifier and the above-mentioned additive, as necessary, are added to water, its pH is adjusted to 3–8 with a pH adjusting agent, and oil, in which difluprednate has been dissolved, is added to give an emulsion. For uniform emulsification, a known means, such as a homomixer, homogenizer, microfluidizer, high pressure homogenizer and the like, may be used.

The composition of the present invention is preferably used as a preparation for local administration to the eye, nose or ear, and more preferably used as an eye drop, nasal drop or ear drop.

The composition of the present invention has superior antiinflammatory action and antiallergic action. In addition, it shows superior transfer of difluprednate in a large amount, uniform drug distribution and extremely reduced levels of uncomfortable feeling and foreign sensation upon administration. In addition, administration of a small dose thereof is sufficient to produce efficacy, whereby side effects can be suppressed. Therefore, it is useful for the prophylaxis and treatment of various inflammatory diseases and allergic diseases, such as allergic conjunctivitis, vernal conjunctivitis, blepharitis marginalis, catarrhal conjunctivitis, uveitis and the like, and it can be beneficially used for local administration to the eye, nose, ear and the like.

The composition of the present invention can be administered safely to mammals (e.g., human, dog, rabbit, cow, horse, monkey, cat, sheep, etc.).

While the dose of the composition of the present invention varies depending on the kind of disease, symptom, age and body weight of patients and the like, when it is administered to an adult, for example, the dose is preferably one or two drops per instillation in one eye according to the state of the disease, as an eye drop containing difluprednate in a concentration of about 0.005–0.1%, wherein the dose frequency is two to four times a day.

The present invention is described in more detail by way of Examples and Experimental Examples, which should not be construed as limiting the invention.

In the following Examples and Experimental Examples, the median size was measured by Shimadzu SALD-2000 laser diffraction apparatus for particle size distribution (dispersion medium: water, refractive index: 1.70–0.20i) upon addition of about 2 ml of the composition to be measured.

EXAMPLE 1

Difluprednate 0.05 g
Castor oil 5.0 g
Polysorbate 80 4.0 g
Concentrated glycerol 2.0 g

Sodium acetate 0.01 g

Boric acid 0.1 g

Sodium edetate 0.02 g

Sorbic acid 0.1 g

Sodium hydroxide suitable amount

Sterile purified water amount to make the total 100 ml (pH 6.0)

Sterile purified water was heated to about 70° C. and polysorbate 80, concentrated glycerol, sodium acetate, boric acid, sodium edetate and sorbic acid of the above formulation were added and dissolved. Its pH was adjusted to 6.0 with sodium hydroxide to give an aqueous phase. Separately, castor oil was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stiring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.06 μm.

EXAMPLE 2

Difluprednate 0.005 g

Castor oil 1.0 g

Polysorbate 80 0.5 g

Concentrated glycerol 2.2 g

Hydroxypropylmethylcellulose 0.1 g

Sodium acetate 0.05 g

Chlorobutanol 0.3 g

Hydrochloric acid suitable amount

Sterile purified water amount to make the total 100 ml (pH 4.0)

Sterile purified water was heated to about 70° C. and polysorbate 80, concentrated glycerol, hydroxypropylmethylcellulose, sodium acetate and chlorobutanol of the above formulation were added and dissolved. Its pH was adjusted to 4.0 with hydrochloric acid to give an aqueous phase. Separately, castor oil was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stirring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.12 μm.

EXAMPLE 3

Difluprednate 0.01 g

Miglyol 10.0 g

Polysorbate 80 5.0 g

Concentrated glycerol 2.2 g

ϵ-aminocaproic acid 0.05 g

Chlorhexidine gluconate 0.005 g

Sodium hydroxide suitable amount

Sterile purified water amount to make the total 100 ml (pH 5.5)

Sterile purified water was heated to about 70° C. and polysorbate 80, concentrated glycerol, ϵ-aminocaproic acid and chlorhexidine gluconate of the above formulation were added and dissolved. Its pH was adjusted to 5.5 with sodium hydroxide to give an aqueous phase. Separately, Miglyol was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stirring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.21 μm.

EXAMPLE 4

Difluprednate 0.1 g

Castor oil 20.0 g

Polyoxyethylene hydrogenated castor oil 60 5.0 g

Concentrated glycerol 2.2 g

Sodium glutamate 0.01 g

Methyl p-hydroxybenzoate 0.02 g

Propyl p-hydroxybenzoate 0.01 g

Sodium hydroxide suitable amount

Sterile purified water amount to make the total 100 ml (pH 5.0)

Sterile purified water was heated to about 70° C. and polyoxyethylene hydrogenated castor oil 60, concentrated glycerol, sodium glutamate, methyl p-hydroxybenzoate and propyl p-hydroxybenzoate of the above formulation were added and dissolved. Its pH was adjusted to 5.0 with sodium hydroxide to give an aqueous phase. Separately, castor oil was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stiring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.06 μm.

EXAMPLE 5

Difluprednate 0.05 g

Castor oil 8.0 g

Polysorbate 80 5.0 g

Polyvinyl alcohol 0.02 g

Concentrated glycerol 2.2 g

Sodium acetate 0.1 g

Benzalkonium chloride 0.01 g

Hydrochloric acid suitable amount

Sterile purified water amount to make the total 100 ml (pH 5.0)

Sterile purified water was heated to about 70° C. and polysorbate 80, polyvinyl alcohol, concentrated glycerol, sodium acetate and benzalkonium chloride of the above formulation were added and dissolved. Its pH was adjusted to 5.0 with hydrochloric acid to give an aqueous phase. Separately, castor oil was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stirring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.06 μm.

EXAMPLE 6

Difluprednate 0.01 g

Miglyol 5.0 g

Polysorbate 80 4.0 g

Concentrated glycerol 2.0 g

Sodium hydrogenphosphate 0.05 g

Sodium edetate 0.01 g

Benzalkonium chloride 0.005 g

Sodium hydroxide suitable amount

Sterile purified water amount to make the total 100 ml (pH 7.0)

Sterile purified water was heated to about 70° C. and polysorbate 80, concentrated glycerol, sodium hydrogenphosphate, sodium edetate and benzalkonium chloride of the above formulation were added and dissolved. Its pH was adjusted to 7.0 with sodium hydroxide to give an aqueous phase. Separately, Miglyol was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stirring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.06 μm.

EXAMPLE 7

Difluprednate 0.05 g

Castor oil 5.0 g

Polysorbate 80 4.0 g

Concentrated glycerol 2.2 g

Sodium acetate 0.05 g

Sodium edetate 0.02 g

Boric acid 0.1 g

Sorbic acid 0.1 g

Sodium hydroxide suitable amount

Sterile purified water amount to make the total 100 ml (pH 5.5)

Sterile purified water was heated to about 70° C. and polysorbate 80, concentrated glycerol, sodium acetate, sodium edetate, boric acid and sorbic acid of the above formulation were added and dissolved. Its pH was adjusted to 5.5 with sodium hydroxide to give an aqueous phase. Separately, castor oil was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stirring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.06 μm.

EXAMPLE 8

Difluprednate 0.01 g

Castor oil 5.0 g

Polysorbate 80 4.0 g

Concentrated glycerol 2.2 g

Sodium acetate 0.05 g

Sodium edetate 0.02 g

Boric acid 0.1 g

Sorbic acid 0.1 g

Sodium hydroxide suitable amount

Sterile purified water amount to make the total 100 ml (pH 5.5)

Sterile purified water was heated to about 70° C. and polysorbate 80, concentrated glycerol, sodium acetate, sodium edetate, boric acid and sorbic acid of the above formulation were added and dissolved. Its pH was adjusted to 5.5 with sodium hydroxide to give an aqueous phase. Separately, castor oil was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stirring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.06 μm.

EXAMPLE 9

Difluprednate 0.002 g

Castor oil 5.0 g

Polysorbate 80 4.0 g

Concentrated glycerol 2.2 g

Sodium acetate 0.05 g

Sodium edetate 0.02 g

Boric acid 0.1 g

Sorbic acid 0.1 g

Sodium hydroxide suitable amount

Sterile purified water amount to make the total 100 ml (pH 5.5)

Sterile purified water was heated to about 70° C. and polysorbate 80, concentrated glycerol, sodium acetate, sodium edetate, boric acid and sorbic acid of the above formulation were added and dissolved. Its pH was adjusted to 5.5 with sodium hydroxide to give an aqueous phase. Separately, castor oil was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stirring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.06 μm.

Experimental Example 1

The transfer into anterior chamber (intraocular transfer) of rabbits was compared between a difluprednate ophthalmic suspension and the composition of the present invention after a single instillation thereof.

A difluprednate ophthalmic suspension, which is a steroidal agent, has been already known to have significant inhibitory effect on rabbits with experimental uveitis. In this Experiment, transfer of difluprednate into anterior chamber (intraocular transfer) was compared between a difluprednate ophthalmic suspension and the composition of the present invention, in an attempt to improve intraocular transfer of difluprednate.

(1) Test Composition

The composition of the present invention and an ophthalmic suspension having the formulations shown in Table 1 were prepared as in the following.

[Composition of the Present Invention]

Sterile purified water (800 ml) was heated to about 70° C., and polysorbate 80 (40 g) and concentrated glycerol (26 g) were added and dissolved to give an aqueous phase. Separately, castor oil (50 g) was heated to about 70° C., and difluprednate (0.5 g) was added and dissolved to give an oil phase. The oil phase was added while stiring the aqueous phase with a homomixer to give a crude emulsion, and sterile purified water was added to make the total amount

1000 ml. This crude emulsion was finely divided in a microfluidizer. Sterilization by filtration gave the composition of the present invention.

[Ophthalmic Suspension]

Sterile purified water (800 ml) was heated to about 70° C. and hydroxypropylmethylcellulose (2 g) was added. After thorough dispersion, the mixture was cooled to about 30° C., and hydroxypropylmethylcellulose was added. Then, sodium acetate (1 g), sodium chloride (8 g) and benzalkonium chloride solution (10 w/v % 0.5 ml) were added and dissolved. Its pH was adjusted to 5.0 with hydrochloric acid and the mixture was sterilized by filtration. Difluprednate (1 g) was added and thoroughly suspended. Sterile purified water was added to make the total amount 1000 ml, whereby the ophthalmic suspension was obtained.

TABLE 1

(in 100 ml)

Formulation	suspension (R.P.1)	composition of the present invention (R.P.2)
Difluprednate	0.1 g	0.05 g
Sodium acetate	0.1 g	—
HPMC (60SH50)	0.2 g	—
Sodium chloride	0.8 g	—
Benzalkonium chloride	0.005 g	—
Hydrochloric acid	suitable amount	—
Sterile purified water	suitable amount	suitable amount
Castor oil	—	5.0 g
Polysorbate 80	—	4.0 g
Concentrated glycerol	—	2.6 g
pH	5.0	6.5
Median size	4.0 μm	0.16 μm

(HPMC: hydroxypropylmethylcellulose)

(2) Test Animal

Male Japanese albino rabbits weighing about 2 kg and having no abnormalities in the eye were used. These rabbits were reared in a rearing chamber set to the conditions of room temperature 23±3° C. and relative humidity 55±10%, each chamber housing one rabbit. The rabbits were fed with solid feed (100 g per day, Labo RG-RO, NIHON NOSAN KOGYO K.K.) and allowed to have a free access to tap water.

(3) Test Method

The test composition (50 μl) was instilled in the eye, and one hour later, the rabbits were slaughtered with pentobarbital. Immediately after slaughter, anterior ocular segment was washed with physiological saline and aqueous humor was taken. Since difluprednate is deesterified at 21 position in aqueous humor and the like and metabolized into DFB (6α,9α-difluoroprednisolone 17-butyrate), DFB was measured by high performance liquid chromatography (HPLC) and taken as an index of difluprednate concentration in anterior chamber. The HPLC conditions were as follows.

HPLC conditions:

column: TSK gel ODS-80Ts

mobile phase: 10 mM $NaH_2PO_4.2H_2O$(pH7)/CH_3CN=55/45

column temperature: 40° C.

flow rate: 1.3 ml/min

wavelength: 240 nm

amount injected: 50 μl

The DFB concentration in the anterior chamber of the eye of rabbits after one hour from a single instillation of the test composition is shown in Table 2.

TABLE 2

DFB concentration in aqueous humor

	test composition	
	suspension (R.P.1)	composition of the present invention (R.P.2)
DFB concentration (ng/ml)	19.15 ± 2.8	42.95 ± 6.5

Each value shows mean ± S.E. (N = 7–8).

When difluprednate was prepared into a composition of the present invention, the amount of intraocular transfer was 42.95 ng/ml, despite the fact that the drug concentration in the composition was half the amount thereof in the suspension. This value was about 2.2 times greater than that in the case of the suspension, and significant difference was found. The above results reveal that the composition of the present invention shows efficacy greater than that afforded by a suspension even in a smaller dose.

Thus, the composition of the present invention has superior antiinflammatory action and antiallergic action.

In addition, the composition of the present invention shows superior transfer to a lesion as well as uniform drug distribution upon administration, as compared to conventional preparations containing difluprednate, so that it shows sufficient efficacy in a smaller dose. The inventive composition is associated with extremely less uncomfortable feeling and foreign sensation upon administration, as compared to conventional preparations containing difluprednate, and it can be administered easily to local sites of eye, nose, ear and the like.

This application is based on application No. 21807/1997 filed in Japan, the content of which is incorporated hereinto by reference.

What is claimed is:

1. A difluprednate emulsion comprising difluprednate, oil comprising a fatty acid ester of glycerol, water and an emulsifier.

2. The emulsion of claim **1**, comprising 10–100,000 parts by weight of oil, 100–100,000 parts by weight of water and 10–100,000 parts by weight of the emulsifier, per part by weight of difluprednate.

3. The emulsion of claim **1**, comprising 10–10,000 parts by weight of oil, 100–50,000 parts by weight of water and 10–10,000 parts by weight of the emulsifier, per part by weight of difluprednate.

4. The emulsion of claim **1**, comprising 10–5,000 parts by weight of oil, 500–50,000 parts by weight of water and 10–5,000 parts by weight of the emulsifier, per part by weight of difluprednate.

5. The emulsion of claim **1**, wherein the fatty acid ester of glycerol is a member selected from the group consisting of castor oil, peanut oil, cotton seed oil, soybean oil, olive oil and a medium chain fatty acid triglyceride.

6. The emulsion of claim **1**, wherein the emulsifier comprises a surfactant.

7. The emulsion of claim **6**, wherein the surfactant is a nonionic surfactant.

8. The emulsion of claim **7**, wherein the nonionic surfactant is a member selected from the group consisting of polyoxyethylene hydrogenated castor oil and a polyoxyethylenesorbitan fatty acid ester.

9. The emulsion of claim **8**, wherein the polyoxyethylenesorbitan fatty acid ester is a member selected from the group consisting of polyoxyethylenesorbitan monooleate,

polyoxyethylenesorbitan monolaurate, polyoxyethylenesorbitan monopalmitate and polyoxyethylenesorbitan monostearate.

10. The emulsion of claim **1** which is an oil-in-water type emulsion.

11. The emulsion of claim **1** which is in the form of an eye drop, a nasal drop or an ear drop.

12. The emulsion of claim **2**, which is an oil-in-water type emulsion.

13. The emulsion of claim **3**, which is an oil-in-water type emulsion.

14. The emulsion of claim **4**, which is an oil-in-water type emulsion.

15. The emulsion of claim **2**, which is in the form of an eye drop, a nasal drop or an ear drop.

16. The emulsion of claim **3**, which is in the form of an eye drop, a nasal drop or an ear drop.

17. The emulsion of claim **4**, which is in the form of an eye drop, a nasal drop or an ear drop.

* * * * *

EXHIBIT 4

US006114319C1

(12) EX PARTE REEXAMINATION CERTIFICATE (4940th)

United States Patent

Kimura et al.

(10) Number: US 6,114,319 C1

(45) Certificate Issued: May 18, 2004

(54) COMPOSITIONS CONTAINING DIFLUPREDNATE

(75) Inventors: **Masako Kimura**, Kakogawa (JP); **Shin-ichi Yasueda**, Kobe (JP); **Masazumi Yamaguchi**, Kobe (JP); **Katsuhiro Inada**, Kobe (JP)

(73) Assignees: **Senju Pharmaceutical Co., Ltd.**, Osaka (JP); **Mitsubishi Chemical Corporation**, Tokyo (JP)

Reexamination Request:
No. 90/006,548, Feb. 13, 2003

Reexamination Certificate for:

Patent No.:	**6,114,319**
Issued:	**Sep. 5, 2000**
Appl. No.:	**09/076,124**
Filed:	**May 12, 1998**

(51) **Int. Cl.**[7] **A61K 31/56**
(52) **U.S. Cl.** **514/177**; 514/912
(58) **Field of Search** 514/177, 912

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

JP 5-43465 2/1993

OTHER PUBLICATIONS

The Merck Index, 12th Ed., p. 1308, 7742 (1996).

Primary Examiner—Frederick Krass

(57) **ABSTRACT**

The present invention relates to a liquid composition comprising difluprednate, oil, water and an emulsifier. The composition of the present invention has superior antiinflammatory action and antiallergic action. The composition of the present invention shows superior transfer to a lesion and uniform drug distribution upon administration, as compared to conventional preparations containing difluprednate, so that it shows sufficient efficacy in a smaller dose. The inventive composition is associated with extremely less uncomfortable feeling and foreign sensation upon administration, as compared to conventional preparations containing difluprednate, and it can be administered easily to local sites of eye, nose, ear and the like.

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

ONLY THOSE PARAGRAPHS OF THE SPECIFICATION AFFECTED BY AMENDMENT ARE PRINTED HEREIN.

Column 5, lines 8–21:

Sterile purified water was heated to about 70° C. and polysorbate 80 (*polyoxyethelyene (20) sorbitan monooleate*), concentrated glycerol, sodium acetate, boric acid, sodium edetate and sorbic acid of the above formulation were added and dissolved. Its pH was adjusted to 6.0 with sodium hydroxide to give an aqueous phase. Separately, castor oil was heated to about 70° C. and difluprednate was added and dissolved to give an oil phase. The oil phase was added while stirring the aqueous phase with a homomixer to give a crude emulsion. This crude emulsion was finely divided in a microfluidizer and sterilized by filtration to give a composition of the present invention. The median size of the oil drop in the composition of the present invention was 0.06 μm.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **5, 11** and **15–17** are cancelled.

Claim **1** is determined to be patentable as amended.

Claims **2–4, 6–10** and **12–14** dependent on an amended claim, are determined to be patentable.

New claim **18** is added and determined to be patentable.

1. A diflupredrnate emulsion *in the form of an eye drop, a nasal drop or an ear drop* comprising (*a*) diflupredrnate, (*b*) *an* oil **[**comprising a fatty acid ester of glycerol**]** *selected from the group consisting of castor oil, peanut oil, cottonseed oil, soybean oil, olive oil and a medium chain fatty acid triglyceride,* (*c*) water and (*d*) an emulsifier.

18. A diflupredrnate emulsion in the form of an eye drop, a nasal drop or an ear drop comprising diflupredrnate, castor oil, water and polyoxyethylene (20) sorbitan monooleate.

* * * * *

EXHIBIT 5

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

Customer No 513

M75N4

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON DC 20006-1021

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(h).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	APPLICATION NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	6,114,319	1551	910	0	09/076,124	09/05/00	05/12/98	04	NO	PAID

Item	Atty Dkt Number
1	279-20606

DIRECT YOUR RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:
Mail Stop: M. Correspondence, Director of the United States Patent & Trademark Office
P.O. Box 1450, Alexandria, VA 22313-1450

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
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Customer No 513 | ISTMT | DATE PRINTED 02/14/2008

WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON DC 20006-1021

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,114,319	**$2,360.00**	**$0.00**	**02/14/08**	**09/076,124**	**09/05/00**	**05/12/98**	**08**	**NO**	**98_0589A**

EXHIBIT 6

SIRiON Therapeutics

November 9, 2006

Janice Soreth, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective & Ophthalmology Products, HFD-520
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: Original IND 75,713
Difluprednate Ophthalmic Emulsion, 0.05% (ST-601A)
Serial No. 0000

Dear Dr. Soreth:

In accordance with 21 CFR 312, Sirion Therapeutics is hereby submitting an original IND for difluprednate ophthalmic emulsion, 0.05% (ST-601A). The clinical development plan for ST601A was discussed at the October 4, 2006 End-of-Phase 2 Meeting between Sirion Therapeutics and members of the Division of Anti-Inflammatory, Analgesic, and Ophthalmology Drug Products. The feedback provided by the Agency at this meeting has guided the design of the proposed 3 studies that are the subject of this IND.

The two Phase 3 studies enclosed herein are each entitled: A Phase 3 Multicenter, Randomized, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Difluprednate in the Treatment of Inflammation Following Ocular Surgery. Also enclosed is the Phase 2b study entitled: A Phase 2b Multicenter, Randomized, Double-Masked Study of the Safety and Efficacy of Difluprednate 0.05% Ophthalmic Emulsion Compared to Prednisolone Acetate 1% Ophthalmic Solution in the Treatment of Anterior Uveitis.

Should you have any questions concerning the enclosed IND, I can be contacted at (813) 496-7325 x236 or by email at cmiller@siriontherapeutics.com.

Sincerely,

Christine Miller, Pharm.D
Chief Operating Officer
Sirion Therapeutics

3110 Cherry Palm Drive, Suite 340 • Tampa, FL • 33619 • Phone: (813) 496-7325 • Fax: (813) 496-7328 • www.siriontherapeutics.com

EXHIBIT 7

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 75,713

Sirion Therapeutics, Inc.
Attention: Christine Miller, PharmD
Chief Operating Officer
3110 Cherry Palm Drive, Suite 340
Tampa, FL 33619

Dear Dr. Miller:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	75,713
Sponsor:	Sirion Therapuetics, Inc.
Name of Drug:	Difluprednate Ophthalmic Emulsion, 0.05%
Date of Submission:	November 9, 2006
Date of Receipt:	November 13, 2006

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before December 13, 2006, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

Please cite the IND number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-796-1202.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Maureen Dillon-Parker
11/20/2006 12:00:42 PM
IND 75,713 Ack Ltr - MDillon-Parker for FVLeSane

EXHIBIT 8

December 21, 2007

Wiley Chambers, MD
Acting Director
U. S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: NDA 22,212
Difluprednate Ophthalmic Emulsion, 0.05% (ST-601)
Original New Drug Application

Dear Dr. Chambers:

Sirion Therapeutics, Inc. (Sirion) hereby submits a New Drug Application (NDA) for Difluprednate Ophthalmic Emulsion, 0.05%. This NDA is being submitted pursuant to 21 CFR 314 and Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act. The drug product will be marketed as a prescription product and is indicated for the treatment of inflammation and pain following ocular surgery.

This NDA was prepared in the ICH Common Technical Document format and is being submitted in electronic format (i.e. DVD)*. Sirion has been granted a waiver of the PDUFA fee for this NDA. A copy of the user fee cover sheet and the FDA letter granting the waiver are provided in Module 1 Section 1.1.3 *User Fee Cover Sheet.*

A list of the facilities identified in this application is also included as an attachment to the Form FDA 356h. All of the facilities are ready for inspection. A notification of this NDA submission has been provided to the District Office in Orlando, FL. A copy of the notification sent to the Orlando District Office is provided in Section 1.3.2 *Field Copy Certification.* In addition, please note that in Module 1 Section 1.12.4 *Request for Comments and Advice*, Sirion is providing proposed tradenames to be reviewed by the Agency.

The information contained in this application is confidential and as such should be handled in accordance with the provisions established in 21 CFR 314.430.

* Sirion certifies that the files on the DVD are virus free and have been scanned with TREND MICRO™ Client/Server Security Agent Version 7.2.

If you have any questions regarding this submission or require additional information, please contact Debra Gessner using the contact information below. For all mail correspondence, please forward to the attention of:

Debra Gessner, MS
VP of Regulatory Affairs
11408 Sorrento Valley Road
San Diego, CA 92121
Tel: (858) 875-9246
Fax: (858) 875-9251
dgessner@siriontherapeutics.com

Sincerely,

Christine Miller, PharmD
Sr VP, Drug Development
Tel: (813) 496-7325 ext 236
Fax: (813) 496-7328
cmiller@siriontherapeutics.com

EXHIBIT 9

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-212

NDA ACKNOWLEDGMENT

Sirion Therapeutics, Inc.
Attention: Christine Miller, PharmD
Senior VP of Drug Development
3110 Cherry Palm Drive, Suite 340
Tampa, FL 33619

Dear Dr. Miller:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Difluprednate Ophthalmic Emulsion, 0.05%

Date of Application: December 21, 2007

Date of Receipt: December 26, 2007

Our Reference Number: NDA 22-212

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 24, 2008, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Jane A. Dean, RN, MSN
Regulatory Health Project Manager
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jane Dean
12/31/2007 03:45:05 PM

EXHIBIT 10

7. Chronology of Significant Activities During the Review Period

IND 75,713

Serial Number	Date	Type of Document/ Communication	Description
---	25-Aug-2006	Letter from FDA	FDA acknowledges Sirion's EOP2 meeting request and assigns a Pre-IND number [75,713]
---	25-Aug-2006	Letter from FDA	FDA grants Sirion an End of Phase 2 (EOP2) [Type B] face-to-face meeting to be held on 04-Oct-2006 at 12pm.
---	01-Sep-2006	EOP2 Pre-Mtg Briefing Document	A EOP2 pre-meeting briefing package was submitted.
---	28-Sep-2006	Email from FDA	FDA sent responses to the question addressed in the EOP2 pre-meeting package.
---	02-Oct-2006	Email to FDA	Sirion sent in clarifications to the FDA comments received on 28-Sep-2006.
---	04-Oct-2006	EOP2 Meeting	EOP2 Meeting held.
000	**09-Nov-2006**	**Investigational New Drug Application**	IND submitted.
---	20-Nov-2006	Letter from FDA	FDA acknowledges receipt of the initial IND.
001	**29-Nov-2006**	**Request for Special Protocol Assessment (SPA)**	Sirion submitted a request for a Special Protocol Assessment (SPA) for a stability study protocol.
002	**06-Dec-2006**	**General Correspondence: Tradename Review**	Sirion submits a request for review of a tradename.
003	**07-Dec-2006**	**Information Amendment: CMC**	Sirion provides 5 study reports that were requested on 04-Dec-2006 by the FDA CMC reviewers.
--	20-Feb-2007	Letter from FDA	FDA provided comments and recommendations that involved Clinical and CMC areas.

Serial Number	Date	Type of Document/ Communication	Description
	09-Mar-2007	IND Safety Report: Initial	A safety report was submitted for a possible, serious, unexpected adverse event that was obtained from a foreign scientific literature report through Senju Pharmaceutical.
0010	**22-May-2007**	**Response to FDA Request for Information/Protocol Amendment-Change in Protocol**	Sirion submits responses to the Agency's questions and comments received on 20-Feb-2007.
---	14-Jun-2007	Letter to FDA: Request for the Waiver of the PDUFA Fee for the NDA	Sirion Therapeutics requests the waiver of the PDUFA fee for the NDA planned for submission by end of 2007.
--	10-Aug-2007	Email from FDA: Pre-NDA Mtg Granted	FDA grants a Pre-NDA meeting scheduled for September 24, 2007.
0015	**05-Sep-2007**	**Information Amendment: Clinical/Statistical Analysis Plan**	Sirion submits the Statistical Analysis Plan (SAP) for Study ST-601A-002a and ST-601A-002b.
--	18-Sep-2007	Email from FDA: Response to Pre-NDA Meeting Questions	FDA forwards responses to the questions posed in the Pre-NDA Briefing package submitted on 14-Aug-2007.
--	27-Nov-2007	Letter from FDA: Granting PDUFA Fee Waiver	FDA grants Sirion a small business waiver of the human drug application fee for NDA 22-212 [difluprednate ophthalmic emulsion].
0020	**31-Jan-2008**	**IND Annual Report**	Sirion submits the Annual Report for the reporting period of Nov 9, 2006-Nov 9, 2007.

7. Chronology of Significant Activities During the Review Period (*Continued*)

NDA 22-212

Amendment Number	Date	Type of Document/ Communication	Description
0000	**21-Dec-2007**	**Original NDA**	Sirion submits NDA 22-212 in eCTD format.
---	31-Dec-2007	Letter from FDA: NDA Receipt Acknowledgement	Letter from FDA acknowledging the receipt of NDA 22-212 on December 26, 2007.
---	18-Jan-2008	Email from FDA: Clinical Questions	Request for Clinical information.
---	18& 22 Jan-2008	Email from FDA: Labeling Questions	Request for Labeling information.
0001	**23-Jan-2008**	**Amendment to Clinical Info. Request of Jan 18, 2008**	Response to Clinical information request.
---	8-Feb-2008	Email from FDA with CMC reviewer questions	Request for CMC information.
---	22-Feb-2008	PDUFA Filing Letter from FDA	Priority review - PDUFA action date: June 26, 2008
---	26-Feb-2008	Email from FDA re: sponsor clarifications to Feb 8 CMC Questions	Clarification received for specific CMC questions raised in NDA CMC review letter/email dated Feb 8, 2008.
0002	**18-Mar-2008**	**Quality Information Amendment (1.11.1) to CMC Comments received February 8, 2008**	Response to CMC comments of Feb. 8, 2008.
---	21-Mar-2008	Email from FDA re: Info request (stats)	FDA requested information regarding the datasets provided.

Amendment Number	Date	Type of Document/ Communication	Description
---	24-Mar-2008	Email from FDA: Info Request	Stats reviewer Information request
---	24-Mar-2008	Email from FDA: Info Request	Requested information regarding Micro (sterility).
---	08-Apr-2008	Email from FDA: Info Request	Requested CMC information.
---	14-Apr-2008	Email from FDA: Info Request	Requested Micro information.
0003	**18-Apr-2008**	**Amendment: 120-Day Safety Update Report**	Submitted 120-Day Safety Update Report.
0004	**25-Apr-2008**	**Quality Information Amendment (1.11.1.2): Response to CMC comments**	Responses to CMC comments of Feb. 8, March 24, April 8 and April 14, 2008.
0005	**28-Apr-2008**	**Efficacy Information Amendment (1.11.3): Response to Comments dated March 5, 2008**	In response to additional information regarding the bioanalytical method and metabolite data obtained for Study 9 and clarification of statistical datasets, respectively.
---	01-May-2008	Email from J. Dean: Request for Submission of Pediatric Plan	Before taking final action on the NDA, J. Dean requested submission of a Pediatric Plan for deferred studies to the NDA.
---	02-May-2008	Email from FDA: Request for Interim Report	Requested an interim report justifying the 80% lower limit for sorbic acid.
---	06-May-2008	Email to/from FDA: IOP Data Request and Response	Requested IOP data.
0006	**08-May-2008**	**Efficacy Information Amendment (1.11.3.2): Pediatric Plan**	Replacement of our request for a waiver of pediatric studies (in Module 1) to a request for a deferral of pediatric studies as outlined in the Pediatric Plan.

Amendment Number	Date	Type of Document/ Communication	Description
0007	**14-May-2008**	**Efficacy Information Amendment (1.11.3.3): Corrected Statistical Analyses**	Submitted corrected statistical analyses.
---	14-May-2008	Email to FDA: Response to Info Request	Response to FDA e-mail information request dated 5/5/08 and follow-up 5/14/08 in regards to particle size.
0008	**15-May-2008**	**Quality Information Amendment (1.11.1.3): Revised Package Insert**	Submitted a revised draft proposed package insert.
---	20-May-2008	Email to FDA: Interim Report	Response to email dated May 2, 2008 requesting interim report (summary document) along with sorbic acid limit data.
0009	**21-May-2008**	**Quality Information Amendment (1.11.1.4): Response to Info Request**	Submitted responses to CMC comments of May 5, 2008.
---	28-May-2008	Email from FDA: Micro Info Request	Request for Micro information.
0010	**30-May-2008**	**Efficacy Information Amendment (1.11.3.4): Response to Info Request**	Response to request of 5/21/08 for additional statistical analyses.
---	02-June-2008	Email from FDA: Add'l Micro Info Request	Request for the test parameters and results for bacterial challenge testing of the 0.2 um Pall Ultipor filters.
---	03-June-2008	Email to FDA: Revised Package Insert	Submitted revised package insert.
---	10-June-2008	Email from FDA: Info Request for Additional Analyses	Request for additional statistical analyses.

Amendment Number	Date	Type of Document/ Communication	Description
0011	**10-June-2008**	**Efficacy Information Amendment (1.11.3.4): Postmarketing Study Commitment**	Commitment to perform postmarketing study in pediatric subjects.
0012	**11-June-2008**	**Quality Information Amendment (1.11.1.5): Response to Info Request**	Response to CMC comments of May 28 and June 2, 2008.
0013	**18-June-2008**	**Quality Information Amendment (1.11.1.6): Response to Info Request**	Response to information requests of May 5 and May 28, 2008 and response to Labeling Meeting changes of June 17, 2008.
0014	**18-June-2008**	**Efficacy Information Amendment (1.11.3.5): Response to Info Request**	Response to request of June 10, 2008 for additional statistical analyses.
0015	**23-June-2008**	**Quality Information Amendment: Revised PI**	Submission of revised Draft Labeling.
---	23-June-2008	Letter from FDA: NDA APPROVAL	Receipt of NDA Approval letter.

EXHIBIT 11

United States Patent and Trademark Office

Assignments on the Web > Patent Query

Patent Assignment Abstract of Title

NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.

Total Assignments: 1

Patent #: 6114319 **Issue Dt:** 09/05/2000 **Application #:** 09076124 **Filing Dt:** 05/12/1998

Inventors: MASAKO KIMURA, SHIN-ICHI YASUEDA, MASAZUMI YAMAGUCHI, KATSUHIRO INADA

Title: COMPOSITIONS CONTAINING DIFLUPREDNATE

Assignment: 1

Reel/Frame: 009369/0995 **Recorded:** 05/12/1998 **Pages:** 4

Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

Assignors:

KIMURA, MASAKO	**Exec Dt:** 04/28/1998
YASUEDA, SHIN-ICHI	**Exec Dt:** 04/28/1998
YAMAGUCHI, MASAZUMI	**Exec Dt:** 04/28/1998
INADA, KATSUHIRO	**Exec Dt:** 04/28/1998

Assignees: SENJU PHARMACEUTICAL CO., LTD.
OSAKA=SHI
5-8, HIRANOMACHI 2-CHOME, CHUO-KU
OSAKA 541-0046, JAPAN

MITSUBISHI CHEMICAL CORPORATION
CHIYODA-KU
5-2, MARUNOUCHI 2-CHOME
TOKYO 100-0005, JAPAN

Correspondent: WENDEROTH, LIND & PONACK
ATTN: MATTHEW JACOB
2033 K STREET, N.W.
SUITE 800
WASHINGTON, D.C. 20006

Search Results as of: 07/31/2008 03:18 PM

If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.0.1
Web interface last modified: April 20, 2007 v.2.0.1